

The Office Action has acknowledged amendments to claims 28, 29, 33, 34, and 48, and the addition of new claims 49-79.

Applicants note that the IDS has been considered by the Examiner.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim objections

The Office Action objects to the specification as containing amino acid sequences without sequence identifiers. Accordingly, Applicants have amended the specification to include proper sequence identifiers, thereby obviating this objection. Applicants have also submitted a sequence listing under 37 CFR 1.821-1.825. Reconsideration and withdrawal of this objection is respectfully requested.

Claim rejections under 35 U.S.C. 112, second paragraph

Claims 28-34 and 49-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite by reciting the phrase “from residues 360-369...,” because there is no frame of reference in the claim or the specification supplied that will uniquely identify the amino acids of claimed position. Applicants respectfully disagree.

The third full paragraph of page 35 indicates that Figure 1 illustrates the 3-D space-filling model of human serum albumin. As the protein sequences of the highly conserved human and mouse serum albumin are well-known in the art before the filing of the instant application (see below), a skilled artisan would readily understand that “residues 360-369” refers to the mature serum albumin residues. To further support this argument, Applicants hereby submit **Exhibit A**, which shows the GenBank entry for the human (Accession No. CAA23753, first associated reference published in 1982, GenBank record last modified on Sept. 12, 1993) and mouse (CAA09617, first associated reference published in 1999, GenBank record last modified on Feb. 2, 2000) serum albumin precursor protein sequences. The first 24 amino acids of the precursors are removed by protease digestion after the Arg-Arg (“R-R”) tryptic cleavage site, as part of the post-translational modification of serum albumins. Therefore, Applicants submit that the well-known

structures of the mature human and mouse serum albumins and the disclosure of the instant application unequivocally provide unique identification for amino acid positions recited in the claims. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim rejections under 35 U.S.C. 112, first paragraph

Claims 28-34, and 49-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Office Action alleges that the specification does not include what biological activity the heterologous polypeptide encoded by the nucleic acid must possess. Thus, the Office Action concludes that a skilled artisan would not know how to make and use the invention because one would not know how to assay and select for the polypeptide since the biological activity of the heterologous peptide has not been defined.

Applicants submit that the Office Action seem to have misinterpreted the claimed invention, which is partly directed to the discovery that serum albumin can serve as a “protein carrier” to a heterologous polypeptide inserted herein, and confers the inserted heterologous polypeptide an increased lifetime (half-life), and thus increased observed biological activity relative to the uninserted heterologous polypeptide (for example, see paragraph bridging pages 5 and 6).

Applicants wish to clarify that the essence of the invention lies not in the peptide that is inserted, but in its fusion with serum albumin. Any nucleic acid encoding peptide sequence which is disclosed in the published literature to have activity, such as the RGD sequence exemplified in the application, can be used to arrive at the claimed invention. The examples of the instant specification demonstrate that certain regions (such as the ones specified in the specification) of serum albumin provides an effective “expression cassette” which allows the expression of such “active heterologous peptides” with increased stability, and retained potency (see above). In fact, the Patent Office routinely allows claims to expression vectors comprising a specific promoter and a heterologous coding sequence without limitation as to the nature of the coding sequence or the peptide it encodes, and the instant claims are conceptually analogous to that situation.

The “40% identity” recited in the specification indicates that the “heterologous peptide” is largely or entirely unrelated to serum albumin. There could be many different types of biologically active heterologous peptides, any of which may be inserted into serum albumin to arrive at the claimed invention. These biologically active heterologous peptides may or may not be related to one another, and they may have a wide range of biological activities, depending on the identity of each specific heterologous peptide. Since each given peptide may possess more than one biological activity (such as the ability to bind one or more other molecules, and the ability of being able to catalyze certain enzymatic reactions, etc.), the biological activity in question may also depend on the specific activity being assayed for. For example, as the specification exemplifies, the heterologous peptide can be an epitope such as the myc epitope, which possesses the biological activity of being able to bind an anti-myc antibody; or the heterologous peptide can be a peptide that can bind a known receptor, such as the $\alpha v \beta 3$ integrin receptor, on endothelial cells and inhibit their growth / proliferation (RGD peptide). Thus, contrary to the Office Action’s suggestion, there is no specific requirement for a particular biological activity, as long as the heterologous peptide possesses at least one biological activity. In addition, contrary to the Office Action’s suggestion, the heterologous peptides may or may not be related to one another, and they do not need to perform the same biological function.

Similarly, it is neither possible nor necessary to specify which regions of amino acid sequences are responsible for biological activity. The claimed invention can be used for virtually any kind of heterologous peptide with any demonstrated biological activity. Thus, it would be impractical if not impossible for Applicants to list each and every biological activity for each and every potentially useful heterologous peptide encoded by nucleic acids. On the other hand, a skilled artisan would not need any such information to practice the claimed invention. In view of the specification, a skilled artisan will appreciate that by inserting a biologically active (functional) peptide or a domain / region thereof into serum albumin, the lifetime of this peptide will be extended when compared to an identical but uninserted peptide or domain. The skilled artisan would already know the biological activity / function of the heterologous peptide encoded by the subject nucleic acid, and the skilled artisan would also know how to assay for that particular biological function. If a region or domain of a peptide is to be inserted, the skilled artisan would know which region / domain of the full-length peptide would possess at least part of the desired

that the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed.

Applicants submit that the Office Action confuses the effects of insertion on the function of a protein (serum albumin) that is host to another protein (heterologous peptide), with the effects of insertion on the inserted protein (heterologous peptide). Even if it is true that effects of a random mutation, even a small deletion or substitution, on the biological function of a specific protein are hard to predict, it does not necessarily follow that the function of an active sequence (heterologous peptide) will be dramatically changed when it is inserted into another protein. In fact, most properly folded proteins or domains maintain their native structure in a fusion protein. For example, the widely used yeast two-hybrid technology depends on the fusion of a DNA binding domain or a transcriptional activation domain to a protein *library* encoded by a cDNA library. If most proteins dramatically changed their function / property in fusion proteins, the yeast two-hybrid library would not be expected to encode many useful proteins, and the yeast two-hybrid technology would not have been nearly as successful as it is today. Another example is phage display, wherein a heterologous peptide or protein is expressed as a fusion protein with a coat protein of bacteriophage, resulting in display of the heterologous peptide on the exterior surface of the virion. In both of these cases, libraries of peptides and proteins can be expressed as fusions, and the apparent success of these technologies provide further proof to the notion that most intact proteins and their functional domains remain functional in fusion proteins.

On the other hand, although it is possible that random insertions may cause structural problems in proteins inserted by other proteins, this is not likely to be the case in the particular case of serum albumin. According to the specification, the structure including the 3-D structure of serum albumin is well-studied (see the 2nd full paragraph of page 7). Particularly, the specification contemplates that several structurally constrained regions may be selected for replacement, on the presumption that structural changes to these regions are unlikely to significantly affect the tertiary structure of the protein as a whole. The fact that several peptides (including the myc epitope and the RGD peptide) have maintained their biological activities when inserted into certain specified serum albumin regions as described in the specification further substantiates this presumption, and the Examiner has not provided evidence that refutes Applicants' experimental data.

biological activity of the intact peptide. In other words, the skilled artisan who wishes to practice the present invention has already identified his or her desired heterologous peptide and biological activity, and needs only to follow the specification in order to prepare the chimeric peptides of the invention and obtain the benefits taught by the inventors, including extended half-life of the biologically active peptide. Thus, the instant specification need not teach what specific biological activity an inserted heterologous peptide possesses, or how to delineate the functional domain of that heterologous peptide which still largely preserves the biological activity of the intact peptide. In fact, the claimed invention does not even recite the requirement of using nucleic acids encoding partial heterologous peptides. Thus, the allegations of the Office Action that “it would be an undue burden to one of ordinary skill in the art to assay for claimed sequences,” and that “it cannot be predicted from the disclosure as to which polypeptides and fragments should be isolated” are unfounded.

The claimed invention is analogous to yeast two-hybrid technology and phage display technology, wherein virtually all kinds of heterologous peptides can be inserted into a yeast two-hybrid vector or a phage display vector (see below). A skilled artisan would not require extensive description of all possible peptides and functions that can be employed as the heterologous peptide to practice the yeast two-hybrid or the phage display technology.

Notwithstanding the fact that assays for isolation of active heterologous peptide are not required to enable the claimed invention, Applicants have described in detail many such assays on pages 21-24. Specifically, the 2nd full paragraph of page 21 refers to U.S.S.N. 09/174,943, filed on October 19, 1998, as containing methods for isolating biologically active peptides. The following pages provide further detailed description as to how such assays can be carried out to obtain suitable active peptides (pages 21-24), for example, peptides with antiproliferative, angiogenic, anti-angiogenic, or anti-infective activities on certain cells.

The Office Action also asserts that protein chemistry is probably one of the most unpredictable areas of biotechnology, and cited several examples to show that even small mutations within certain protein sequences may lead to potentially inactivating mutations that dramatically affect the biological activity and characteristic of a protein. In addition, the Office Action asserts

Based on the above argument, Applicants submit that the specification has provided ample working examples that reasonably correlate with the full scope of the claimed invention, and that a skilled artisan would be able to practice the claimed invention without undue experimentation. Thus, the enablement requirement of 35 U.S.C. 112, first paragraph is met. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 58 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the Office Action alleges that “the specification does not disclose any objective evidence regarding the isolation of and assaying of the claimed nucleic acid, the successful binding of a heterologous polypeptide to an orphan receptor.” Furthermore, the Office Action asserts that there are no other disclosed examples that convey to a skilled artisan that Applicants were in possession of the claimed nucleic acid, and that there is no actual reduction to practice, sufficient descriptive information including definitive structural features critical to activity, or complete detailed description of the function of claimed invention indicating that the claimed nucleic acid was indeed isolated, produced, and assayed for the uses disclosed. Applicants respectfully disagree.

Applicants respectfully remind the Examiner that the final guidelines for 35 U.S.C. 112 clearly state that there is a strong presumption that the specification as filed provides adequate written description support for the claimed invention. Pursuant to MPEP 2163.02 (8th edition released in August, 2001) “An objective standard for determining compliance with the written description requirement is, ‘does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.’... Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed.... An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention.... Possession may be shown in a variety of ways including

description of an actual reduction to practice, or by showing that the invention was ‘ready for patenting’ such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete.” (emphasis added). MPEP 2163.03 also states that “rejection of an original claim for lack of written description should be rare.” A disclosure as filed is *prima facie* adequate. To support a rejection, the PTO has the burden of showing why Applicants’ evidence is insufficient. In any case where lack of written description is found, the PTO should cite documentary evidence in support of the finding.

In view of the guidelines recited above, and the arguments presented below, Applicants respectfully submit that the Office Action has failed to fully consider the factual evidence submitted by Applicants in light of the strong presumption due to the disputed terms – all of which were included in the original claims as filed – and has not shown why Applicants’ supporting evidence is insufficient. Neither does the Office Action provide documentary evidence or convincing technical reasoning as required by the Guidelines (MPEP 2163.02) to rebut the presumption in favor of the Applicants.

Particularly, Applicants submit that Applicants have shown possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Specifically, pages 2-5 of the specification as well as the original claims 1-27, and 34 describe in detail the structure of various forms of the chimeric serum albumin (SA) polypeptides encoded by the claimed nucleic acids. For example, the 1st full paragraph of page 2 reads:

One aspect of the present invention provides a chimeric polypeptide comprising a biologically active heterologous peptide fragment inserted into a serum albumin protein or a homolog thereof. The heterologous peptide fragment may optionally replace a portion of the serum albumin protein sequence. A peptide fragment which replaces a portion of the serum albumin protein sequence need not be of the same length as the fragment it replaces. A chimeric polypeptide according to this aspect may include more than one heterologous peptide fragment which replaces a portion of the serum albumin protein sequence. The included fragments may be identical, may be distinct sequences from a protein unrelated to serum albumin protein, or may be distinct sequences of unrelated origin.

The 3rd full paragraph of page 3 reads:

In another embodiment, the heterologous peptide sequence is capable of binding to a cell surface receptor protein. Examples of such a receptor protein include a G protein-coupled receptor, a tyrosine kinase receptor, a cytokine receptor, an MIRR receptor, and an orphan receptor. (emphasis added)

The last paragraph of page 3 reads:

The invention also comprises a nucleic acid sequence which encodes a chimeric polypeptide as described above.

The remaining paragraphs of the same section summarize the structures of the various chimeric polypeptides encoded by the claimed nucleic acids, and the characteristics (length, half-life, ability to bind to various receptors, etc.) of the heterologous peptides inserted therein.

Furthermore, contrary to what the Office Action alleges, Applicants have demonstrated possession of the claimed invention by describing examples of actual reduction to practice. The example section set forth at least one specific example demonstrating how the chimeric peptides encoded by the claimed nucleic acids can be made and used. Specifically, the example shows that the RGD peptide retained its biological activity when inserted into SA. The results are illustrated by Figure 3.

The Office Action alleges that the specification does not disclose the isolation of a claimed nucleic acid encoding heterologous peptide, or assay methods to measure biological activity. Applicants submit that it is the nucleic acid encoding chimeric SA polypeptide that is claimed, not the *isolation* of a nucleic acid encoding a heterologous peptide or *assaying* of the biological function of the claimed nucleic acid. These entities are well known in the art, and thus need not be described in detail in the specification; one of skill in the art would readily envision the full scope of these terms without the need for voluminous explication. Thus, to meet the written description requirement, the specification does not need to describe either the isolation of a nucleic acid encoding a heterologous peptide, or to provide a way of assaying the biological function of the claimed nucleic acid.

Applicants respectfully remind the Examiner that the Supreme Court recently articulated a standard whereby the PTO must establish a rational connection between the agency's fact-findings and its ultimate action. *Dickinson v. Zurko*, 119 S.Ct. 1816 (1999). In light of Applicants' arguments of record, and the presumption in favor of Applicants, it is respectfully asserted that the

present rejection is not supported by substantial evidence, and as such, fails to rise above the "arbitrary, capricious" standard applied under the "substantial evidence" test of Section 706(2)(E) of the Administrative Procedure Act. The Office Action has not cited any relevant art nor relied on any other fact-finding results to rebut the presumption in favor of Applicants.

Similarly, the same argument applies to the Office Action's allegations that Applicants have not disclosed any objective evidence regarding the successful binding of a heterologous polypeptide to an orphan receptor. In contrast, In fact, the specification provides detailed description of various types of orphan receptors to which a heterologous peptide may bind. For example, the 1st full paragraph of page 24 reads:

Preferred EPH receptors include *eph*, *elk*, *eck*, *sek*, *mek4*, *hek*, *hek2*, *EEK*, *erk*, *tyro1*, *tyro4*, *tyro5*, *tyro6*, *tyro11*, *cek4*, *cek5*, *cek6*, *cek7*, *cek8*, *cek9*, *cek10*, *bsk*, *rtk1*, *rtk2*, *rtk3*, *myk1*, *myk2*, *ehk1*, *ehk2*, *pagliaccio*, *hik*, *erk* and *nuk* receptors.

As a skilled artisan will appreciate, EPH receptors are one of the largest families of orphan receptors known to date, and they comprise the largest subfamily of receptor tyrosine kinases. Most, if not all, of these orphan receptors now have identified ligands now known as "ephrins" according to the EPH Nomenclature Committee (see Eph Nomenclature Committee: Unified nomenclature for the Eph family receptors and their ligands, the ephrins. Cell 90: 403-404, 1997. submitted herewith as **Exhibit B**). Therefore, this knowledge is well known in the art, and thus need not be described in detail in the specification ("Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986)." MPEP 2163); one of skill in the art would readily envision the full scope of these terms without the need for voluminous explication.

Furthermore, the example section provides a working example of an MSA-RGD chimeric peptide that binds to the integrin receptor $\alpha v \beta 3$. A skilled artisan will readily appreciate that any usual ligands of an orphan receptor (such as ephrin-A1 for EphA1 receptor, Ephrin-A2 for EphA2 receptor, etc.) can be the "heterologous peptide" inserted into SA. Again, the Office Action has failed to provide any documentary evidence or convincing technical reasoning as required by the Guidelines (MPEP 2163.02) to rebut the presumption in favor of the Applicants.

For the reasons presented above, Applicants submit that the specification has provided not only a detailed description of the claimed invention, but also numerous working examples (actual reductions to practice). Thus, all pending claims as amended fully comply with the written description requirement. Accordingly, reconsideration and withdrawal of rejection under 35 U.S.C. 112, first paragraph is respectfully requested.

CONCLUSION

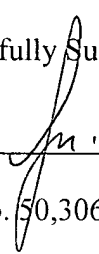
For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945**. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

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Respectfully Submitted,



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